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Running title: Plasticity as a biomarker of neurotoxic damage

Keywords: methylazoxymethanol, complex environment, cortical plasticity, biomarker, developmental neurotoxicology

Abbreviations
ANOVA, analysis of variance
EC, complex environment
EPA, Environmental Protection Agency
GD, gestational day
GLM, general linear model
IC, individual cage
i.p. intraperitoneal
MAM, methylazoxymethanol acetate
mg/kg, milligrams/kilogram
NIH, National Institutes of Health
p, p (probability) value
OC, occipital cortex
SE, standard error
N, subject number
mm, millimeters
r, correlation coefficient

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Abstract

Millions of children are exposed to low levels of environmental neurotoxicants as their brains are developing. Conventional laboratory methods of neurotoxicology can detect maldevelopment of brain structure but are not designed to detect maldevelopment of the brain's capacity for plasticity that could impair learning throughout life. The environmental complexity (EC) paradigm has become classic for demonstrating the modifications in brain structure that occur in response to experience and thus provides a set of indices for plasticity in the healthy brain. Here, we test the hypothesis that if degradation of experience-dependent cortical plasticity is used as a biomarker, then developmental neurotoxic effects will be detected at doses below those that alter cortical morphogenesis overtly. Pregnant Long Evans hooded rats received a single injection of either saline vehicle, 1, 5, 10 or 25 mg/kg of the well-characterized developmental neurotoxicant methylazoxymethanol acetate (MAM) on the 16th or 17th day of gestation. On postnatal day 35-39, male offspring were assigned to either a complex environment (EC) or an individual cage (IC) for 28 days to stimulte neuroanatomical plasticity. This response was measured as the difference between the thickness of visual cortex of IC and EC littermates at a given dose. The threshold dose for significant reduction of cortical thickness was 25 mg/kg, but the threshold dose for failure of plasticity was much lower, and could be detected at 1 mg/kg, the lowest dose used. No other method of assessment has detected lasting effects of prenatal exposure to MAM at such a low dose. These data suggest that this simple test of plasticity could be an efficient way to detect subtle neurotoxic damage to the developing brain.